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NOVEL METHODS AND FORMULATIONS FOR ADMINISTRATION OF ACTIVE AGENTS

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Abstract of WO03011214

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(71) Applicant *(for all designated States except US)*: **ROYER BIOMEDICAL, INC.** [US/US]; 4580F Mack Avenue, Frederick, MD 21703 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ROYER, Garfield, P.** [US/US]; 20858 Green Garden Road, Upperville, VA 20185 (US). **MANDA, Joseph, A.** [US/US]; 9801 Pebble Beach Court, Ijamsville, MD 21754 (US).

(74) Agent: **DAVIDSON, Bryan, H.**; Nixon & Vanderhye P.C., Suite 800, 1100 North Glebe Road, Arlington, VA 22201-4714 (DE).

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(54) Title: NOVEL METHODS AND FORMULATIONS FOR ADMINISTRATION OF ACTIVE AGENTS

(57) Abstract: This invention relates generally to the production and use of inorganic-conditioning agent complexes for the controlled release of compounds including medicinals. Advantageously, the inorganic used is calcium sulfate and the conditioning agent is calcium stearate.

Novel Methods and Formulations for Administration of Active Agents

Field of the Invention

The subject invention relates to novel compositions and methods for delivery of active agents.

Background of the Invention

Polymer matrices designed for controlled release of bioactive compounds can be non-resorbable or resorbable. In general, resorbable means degradable in the body by erosion from the surface or breakdown from within. The mechanism can involve either a chemical reaction, such as hydrolysis, or dissolution.

Non-resorbable polymers, such as polymethylmethacrylate, have been used for antibiotic delivery. These materials suffer from the disadvantage that they must be retrieved, which involves a second intervention and entails the risk of infection (HW Bucholz, et al., (1970) *Chiburg*, **43** , 446).

Resorbable polymer matrices for controlled release are usually based on an oxygenated monomer, which is condensed in organic solvent to yield the polymeric product. The bioactive agent and the polymer are then combined in such a way as to give a timed-release formulation. The combination of active ingredient and polymer often involves organic solvents as well. The use of organic solvents is a decided disadvantage, especially when large-scale production is required. Toxic residues of organic solvents are a concern. Proteins and many polypeptides are incompatible with organic solvents.

The types of polymers in this category include:

-polyesters
-polyanhydrides
-polyketals
-poly(orthoesters)
-polyurethanes

(Burkersroda, FV and Goepferich, AM in *Biomedical Materials*, T Neenan, M Marcolongo and RF Valentini, eds. (1999), page 23, Materials Research Society, Warrendale Pa.).

Naturally occurring proteins may be used as structural components in drug-delivery matrices (Royer, US Patent 4,349,530; Royer, US Patent 5,783,214; Lee, *Science* (1981) 233-235). One deficiency of proteinaceous delivery matrices is that they can exhibit instability especially in environments where an inflammatory reaction is present such as a site of localized sepsis.

WO 99/15150 discloses a stable, yet practical composition for use in inflamed sites comprising an inorganic compound, a matrix polymer and/or a complexing agent. This

composition has the advantage of being biocompatible but, unlike synthetic organic polymers, no non-aqueous solvents are required in the preparation. The drug is incorporated as a solid or as part of the matrix polymer solution. The material can also be used as a cement, that is, it can be injected directly into a lesion and allowed to solidify *in situ*.

The oral administration of active agents such as therapeutics to horses, food animals or domestic pets can be problematic. For large animals, such as livestock and horses, commercial ivermectin is an antiparasitic which has been formulated in liquid and paste form. The liquid consists of surfactants that form micelles in which the insoluble ivermectin molecule is isolated from and dispersed in water. Liquids can be injected which is inconvenient and has accompanying risks such as infection and irritation at the injection site. Further, horse owners are often averse to giving intra-muscular or subcutaneous injections. Alternatively, the liquid can be drenched which means squirted into the back of the horses mouth or by "tubing," i.e., naso-gastric intubation, generally a procedure reserved for veterinarians. The paste formulation of ivermectin is also injected into the back of the horse's mouth. Unfortunately, many horses resist this procedure and some will spit out the paste. Horse owners and veterinarians are sometimes required to restrain the horse with a twitch or other device in order to use the paste reliably. As a minimum, a halter is required in the vast majority of horses. All of the above aforementioned procedures require restraint of the horse. For deworming horses, the recommended regimen for ivermectin is once every 6-8 weeks. The deworming is accomplished either by the horse owner, by stable workers, or in rare cases by a veterinarian. Because of the inconvenience of using paste dewormers, owner compliance can be a problem. The second problem involves inaccurate dosing. In the process of injecting the paste into the horse's mouth, the horse will throw its head and discharge some of the paste or refuse to swallow. The user of the paste syringe is then required to make a decision as to how much was lost.

Ivermectin is a semi-synthetic derivative of abamectin. It typically contains at least 80% of 22,23 dihydroavermectin B1a and 20% of 22,23-dihydroavermectin B1b. As used herein, the term "ivermectin" includes the various formulations used by those skilled in the art. Ivermectin is lipophilic with very low water solubility (4mcg/ml). As expected, ivermectin strongly binds to serum proteins. With a molecular weight of 875 and 20 chiral centers, it is a large complex structure containing a lactone macrocycle along with two gycosidic linkages. The compound is epimerized by base and UV light (see Ivermectin and Abamectin (1989) WC Campbell, Ed., Springer-Verlag, NY).

Use of ivermectin as an antiparasitic is attractive in that it acts by disruption of gamma-aminobutyric acid mediated neurotransmission in parasites such as nematodes and arthropods but does not affect mammals. Higher organisms have receptors for gamma-aminobutyric acid but only in the CNS, not penetrable by ivermectin. The spectrum of ivermectin is quite broad and includes virtually all parasites that infect horses except tapeworms and hookworms, which are relatively uncommon. Fortunately, ivermectin-resistant strains of equine parasites have not evolved. Two other very attractive features of ivermectin include a high margin of safety and the requirement of very low dosages. Cattle were treated with 30 times the recommended dose with little or no toxicity. The dosage in the horse and other livestock is 200 mcg/kg. The recommended frequency of dosing for horses is once every 6-8 weeks.

Domestic animal (egs. cats and dogs) use of ivermectin is for the prevention of canine and feline heartworm disease (*Dirofilaria immitis*) and for the treatment of intestinal hookworms, roundworms, and whipworms. Administration typically entails dosing the ivermectin to the cats and dogs on a once a month regime at a minimum of 6.0 mcg per kilogram of body weight (2.72 mcg/lb). The current dosage forms available for ivermectin include both an extruded meat-by-product and a compressed chewable tablet. In both cases, the palatability of the product is poor.

Objects of the Invention

It is an object of this invention to provide a safe resorbable delivery system that can be designed and fashioned to provide controlled release of bioactive substances over a pre-determined time-course.

It is an object of this invention to provide a delivery matrix which when installed as an injectable liquid can solidify in the presence of moisture.

It is an object of this invention to provide a delivery matrix with enhanced stability in acidic and neutral media.

It is an object of the present invention to provide a delivery matrix with improved molecular complexing agents.

It is an object of the invention to provide a safe, effective, and convenient dosage form of ivermectin for treatment and prevention of parasites in mammals such as horses.

It is an object of the invention to provide a safe, effective, and convenient dosage form of an anti-infective or anti-parasitic in mammals.

It is an object of the invention to provide a safe, effective, and convenient dosage form of a nutraceutical or vitamin in mammals.

Summary of the Invention

The subject invention relates to a delivery matrix formed by mixing:
an inorganic compound capable of undergoing hydration and/or crystallization, plus,
a conditioning agent which improves stability, extends the residence time, and provides for control of the release profile, and optionally, a matrix polymer, and/or
a complexing agent.

Mixing a bioactive agent with the above components results in a solid composition that is capable of providing sustained release of said agent over a predetermined time period.

The subject invention also relates to a feed composition comprising: a) feed, b) a solid composition comprising an active agent dispersed throughout a solid matrix hydration

reaction product of an aqueous mixture comprising said active agent, an inorganic compound capable of undergoing hydration, a conditioning agent, and/or a matrix polymer, and/or a complexing agent, and uses thereof.

Detailed Description of the Invention

The subject invention relates to compositions and methods for delivery of active agents. Safety, convenience, and reliability of dosing are advantages of the instant invention over other dosage forms.

The inorganic compound-conditioning agent composites described herein are resorbable by dissolution. No acid is produced as opposed to hydrolytic erosion of polymer matrices such as polyesters.

The inorganic-conditioning agent composite described herein requires no organic solvent in matrix preparation or drug loading. No acid is produced on erosion so it is useful for orthopedic applications. The inclusion of the conditioning agent and advantageously the matrix polymer imparts control over the release profile of the active ingredient and distinguishes this material from unadulterated plaster of Paris which is rigid and safe but is otherwise lacking in performance (D Mackey, et al. (1982) *Clin. Orthop.* **167**, 263; GW Bowler, et. al. (1994) J. Trauma, **36**, 331). The matrix described in commonly-owned WO 99/15150 may also contain a complexing agent to retard the release of the active ingredient.

The matrix formulation of this invention contains improved hydrophobic complexing agents, e.g., pamoates, and conditioning agents that can serve as water repellants. Water repulsion of these matrices allows for set-up in an aqueous environment. In fact, when a conditioning agent is present, the matrix will solidify when totally submerged. This trait is important when the material is used in orthopedic or dental applications. Examples include filling of periodontal defects or treating an osteomyelitic lesion. Also, the lifetime in the environment, or the body, is extended. This extended residence time is important in the delivery profile. Multiple formulations with different residence times can be combined. The resultant release profile has a desirable form and resembles zero-order. When hydrophobic complexing agents and conditioning agents are used with hydrophobic medicinal agents, the release profiles can be controlled.

The Compositions

Entrapment of active substances within the resorbable biocompatible matrix described herein yields a delivery system, which permits controlled and localized release of a bioactive agent. Inorganic compounds such as $CaSO_4$-1/2 H_2O (calcium sulfate hemihydrate) can be combined with a polymer in the presence of a bioactive agent to produce a solid which constitutes a biocompatible and resorbable delivery matrix (See WO 99/15150—the entire contents of which is incorporated by reference herein). The matrix polymer increases the internal viscosity of the device, which slows the efflux of the bioactive agent.

The delivery system is formed by mixing:

-an active agent
-an inorganic compound capable of undergoing hydration and/or crystallization, plus
-a conditioning agent, and/or
-a matrix polymer, and/or
-a complexing agent.

In one embodiment, the resulting composition can then be added to food or feed. The active agent is mixed with one of the inorganic compound, conditioning agent, matrix polymer and complexing agent, prior to mixing with food or feed.

The use of a conditioning agent such as calcium stearate provides improved stability and added control of the release profile and residence time. Water repulsion can also stabilize the solid dosage form with extension of residence time. Calcium stearate is included at a rate of up to 30 % w/w, advantageously 2.5-20% w/w, based on the amount of inorganic compound, e.g., calcium sulfate hemihydrate. Even higher levels of calcium stearate are obtainable depending on the nature and amounts of other components.

The nature and amount of matrix polymer, the relative proportions of calcium sulfate hemihydrate and matrix polymer (liquid), the complexing agent, and the nature and amount of the conditioning agent permit the adjustment of the release profile and residence time of the matrix.

In the case of poorly water-soluble substances such as ivermectin, the matrix biopolymer can serve as a solubilizing agent. The polymer can bind the active ingredient and carry it to the intestinal mucosa for absorption and uptake into the bloodstream. The matrix polymer can also act to stabilize the active ingredient.

1. Inorganic Compounds

Calcium sulfate $1/2H_2O$ (hemihydrate) (hh) is the preferred inorganic component. The hemihydrate takes up water and crystallizes as the higher hydrate. Unadulterated calcium sulfate matrix exhibits poor drug release profiles. With conditioning agents, and optionally matrix polymers and complexing agent-active agent complexes the release profiles are improved. Other inorganics can be employed such as calcium silicates, aluminates, hydroxides and/or phosphates (see pages 72, 95, 327 in Reference Book of Inorganic Chemistry (1951) Latimer, W.H., and Hildebrand, J.M., Macmillan, New York, hereby incorporated by reference in its entirety).

2. Conditioning Agents

Conditioning agents are used to slow the erosion rate and permit solidification in the presence of moisture (repels water). All conditioning agents have a hydrophobic moiety. Calcium stearate is an advantageous choice for a conditioning agent that meets the criteria of safety and efficacy. Other calcium salts are useful in this regard. Examples include saturated and unsaturated carboxylic acids, aromatic carboxylic acids, corresponding phosphates, phosphonates, sulfates, sulfonates, and other compounds containing a hydrophobic moiety

with a negatively charged anion. Salts of undecylenic acid are useful, in that they provide stability and also antifungal action. The use of calcium as the cation is advantageous but other cations will suffice; the group includes, but is not limited to, zinc, magnesium, aluminum and manganese. The generalized chemical structure can be illustrated as follows:

R-X-M

where R is alkyl, alkenyl, alkynyl or aryl,
where X is a carboxylate, a carboxylic acid, an aromatic carboxylic acid, a corresponding phosphate, a phosphonate, a sulfate, or a sulfonate, and
where M is a metal ion such as calcium, zinc, magnesium, aluminum or manganese.
An example is calcium stearate, $(CH_3\ [CH_2]_{16}COO^-)_2Ca^{2+}$
In this case $R = CH_3[CH_2]_{16}$, $X = COO^-$, and M is the metal ion Ca^{2+}. Cationic conditioning agents can also be employed, i.e.,

R-P-Y

where R = alky, alkenyl, alkynl or aryl,
where P = ammonium, or alkyl ammonium, and
where Y = sulfate or phosphate.

3. Matrix Polymers
The preferred matrix polymers for medical use are
biocompatible (non-toxic, non-allergenic, non-immunogenic)
water soluble
compatible with other components in the formulation

Examples of matrix polymers include chondroitin sulfate, dextran (1-50%), hyaluronic acid (e.g., 1-5%), dextran sulfate, DEAE –dextran, pentosan polysulfate, polyethylene glycol, polyvinylpyrrolidone, proteins such as collagen (gelatin) and fibrinogen and polypeptides. In an advantageous embodiment, a crosslinking agent is added to the matrix polymer. The addition of the crosslinking agent causes a reaction which leads to a higher molecular weight matrix polymer which increases viscosity. Diffusion is thereby inhibited. See Royer U.S. Patent No. 5,783,214 hereby incorporated by reference in its entirety. Counterions, are advantageously sodium or calcium. Chitosan as well as cationic polypeptides, polylysine, and polyarginine are examples of useful polymers that are positively charged at neutral pH.

The function of the matrix polymer is to control the viscosity, which is dependent on the nature, molecular weight and concentration of the polymer. The rationale for using polymers and polymeric complexing agents is based on Stokes law:

D is proportional to 1/Mv

D = the diffusion coefficient
M = the molecular weight of the medicinal
v = the viscosity of the medium

4. Complexing Agents
To the extent that polymeric complexing agents increase the effective molecular weight of the active ingredient, the rate of efflux is slowed according to D 1/Mv. Complexing agents can be polymers or small molecules. The agents can form ionic bridges or hydrophobic

bonds with the molecule to be delivered. The complexes involving the bioactive agents can range from sparingly soluble to soluble. Disodium pamoate is a good example of a complexing agent that forms sparingly soluble adducts with cationic bioactive ingredients. Disodium methylene disalicylate is a similar molecule to disodium pamoate that performs the same function. Procaine and benzathin can be used to reduce the solubility and rate of efflux of anionic bioactive agents. Additional complexing agents are presented in WO 99/15150.

5. Active Agents and Uses of the Compositions of the Invention

Medicinals (both non-protein drugs and medicinal proteins) useful with the matrices of the invention are presented in WO 99/15150. Therapeutics, antigens, antibodies, adjuvants, and regulatory molecules such as hormones exemplify bioactive agents that are useful.

The matrix prepared as described above can be combined with soluble bioactive agent and optionally a complexed bioactive agent, to provide an initial burst and intermediate control.

Clindamycin-HCl free in solution, plus clindamycin-pamoate (as a sparingly soluble salt complex), plus clindamycin-pamoate encapsulated as above in the calcium sulfate-conditioning agent-polymer matrix comprise a three component system for delivery of clindamycin with a desirable release profile. This combination has been employed to provide an antibiotic depot in cats and dogs. Alternatively, a depot can be formed of the soluble drug and the complexed drug alone.

Another embodiment of the invention is a formulation containing a mixture of Drug calcium sulfate, Drug calcium sulfate-calcium stearate 2.5%, Drug calcium sulfate-calcium stearate 5.0% and Drug calcium sulfate-calcium stearate 10%.

Antibiotic formulations can be used to treat localized infections such as osteomyelitis, joint infections, and diabetic foot ulcers. Subsequent to surgical debridement (drainage), beads (e.g., 3mm), microbeads, or cement is installed at the site of the infection. Infected screw channels in bones can be treated successfully using amikacin cement. Microbeads containing amikacin pamoate are effective in the treatment of joint sepsis. For dead space management following surgical repair of fractures, antibiotic cement can be used.

Another use of antibiotic matrix involves dentistry. Periapical abscesses can be treated with microbeads containing amikacin/clindamycin. Doxycycline cement can be administered by syringe to fill periodontal defects (*See* Example 16).

Various anti-infectives useful in conjunction with the formulations of the invention include gentamicin, clarithromycin, doxycycline minocycline and lincomycin, amikacin, penicillin, cefazolin, ciprofloxacin, enrofloxacin, norfloxacin, silver sulfadiazine, imipenem, piperacillin, nafcillin, cephalexin, cefoperazone, vancomycin, tobramycin, nystatin, and amphotericin B or salts thereof (e.g., pamoate salt). Forming the pamoate (a complexing agent) of anti-infectives to form complexes such as amikacin pamoate, clindamycin and gentamicin pamoate, are useful alone or in the formulations of the invention.

Cis- platin, and other anti-neoplastic agents, can be delivered locally with beads (e.g., 3mm) or with microbeads prepared as described herein. In one embodiment, localized administration is beneficial in that systemic toxicity is eliminated but concentrations in the area of cancerous tissue are high.

Vaccine antigens can be delivered with the system of the invention, for example, with microbeads (i.m. injection). The system of the invention can also be used for formulation of nucleic acid vaccines.

Antiparasitics

Antiparasitics such as macrocyclic lactones can be delivered using the delivery system of the invention. Ivermectin has been formulated in a micro-granular form as described in detail below. Briefly, ivermectin is finely ground and blended with calcium sulfate hemihydrate. Calcium stearate is included to the extent of 5-10% (w/w) of the calcium sulfate hemihydrate. A solution of a pharmacologically acceptable polymer such as polyethyleneglycol is added to the mixture of powders. The calcium sulfate hemihydrate dissolves and is converted to calcium sulfate dihydrate, which crystallizes; the ensuing solid mass is allowed to dry at room temperature. Milling and seizing yields the dosage form.

For a 1250 pound horse 1.68 g of the ivermectin formulation is used as a feed top-dress to deliver 200mcg/kg. Strongyl eggs are dramatically reduced in the feces of treated horses. Profiles showing blood levels of ivermectin vs time are virtually identical to those generated by other FDA approved dosage forms.

Moxidectin can also be used.

Anti-infectives

As a top dressing or for oral use, various orally active anti-infectives useful in conjunction with the formulations of the invention include lincomycin, penicillin, ciprofloxacin, enrofloxacin, norfloxacin, nafcillin, cephalexin, orally active cephalosporin.

Vitamins/Micronutrients

All animal health vitamins can be included in the delivery system for administration to animals. Examples include: vitamin C, vitamins A and D, vitamin B12, and equine hoof growth supplements.

Minerals

Animal health minerals can be included in the feed compositions of the invention. Examples are copper sulfate, organic iodide, potassium, etc.

Other Agents

The delivery system of the invention can also be used to deliver non-medical bioactive agents include sterilants, pheromones, fungicides, algicides, growth regulators, nutraceuticals, repellents, and nutrients. (*See* also WO 99/15150).

* * *

A representative formulation follows:

Ingredient	Amount
Ivermectin	100 mg
Calcium sulfate hemihydrate	0.9g
Calcium stearate	0.05g
Polymer solution (PEG) (10% w/v)	0.6 ml

When the amount of calcium sulfate hemihydrate is set at about 1g the amount of bioactive substance is set in the range of 1-300mg. The concentration of polymer can be 10, 20, 30, 40, as high as 50 % (w/v). The conditioning agent is present in the range of 5-30% (w/w) based on calcium sulfate. The ratio of liquid/solid is 0.4-0.8, preferably 0.6.

The calcium sulfate hemihydrate can be sterilized by dry heat (e.g. 140 for 4hr); the polymer solution is sterilizable by filtration (0.2-micron filter). Terminal sterilization by gamma irradiation at 15-18 kGy is also effective.

A compilation of useful formulations is shown below in Table 1.

Table 1. Useful formulations containing calcium sulfate hemihydrate and the conditioning agent calcium stearate

Formulation	$CaSO_4$-hh/ CaStearate	Matrix Polymer	Medicinal
A.	1g (95/5)	0.6 ml (10% PEG, 8,000)	160mg amikacin pamoate*
B.	1g (95/5)	0.6 ml (10%dextran sulfate)	200mg amikacin sulfate
C.	1g (95/5)	0.6 ml (10%dextran sulfate)	200mg amikacin caprylate*
D.	10g (95/5)	6 ml (10% PEG, 8,000)	2g cefoperazone
E.	1 g (95/5)	0.6ml (20% PEG, 8,000)	200mg cefoperazone
F.	1g (95/5)	0.6 ml (10% PEG, 8,000)	160mg clindamycin pamoate*
G.	1g (95/5)	0.6 ml (10% PEG, 8,000)	260mg enrofloxacin
H.	1g (95/5)	0.6 ml (10% PVP, K-30)	160mg silver sulfadiazine
I.	1g (95/5)	0.6 ml (10% PEG, 8,000)	240mg ofloxacin
J.	1g (95/5)	0.6 ml (3% fibrinogen)	240mg ofloxacin
K.	1g (95/5)	0.6 ml (10% PEG, 8,000)	100mg betamethasone

L.	1g (95/5)	0.6 ml (10% PEG, 8,000)	120mg *cis*-Pt
M.	1g (95/5)	0.6 ml (10% PEG, 8,000)	120mg triclosan
N.	1g (90/10)	0.6 ml (10% dextran sulfate)	160mg muramyl dipeptide
O.	1g (90/10)	0.6 ml (10% dextran sulfate)	160mg chloroxylenol
P.	1g (90/10)	0.6ml (10% PEG, 8,000)	160 mg leuprolide acetate
Q.	1g (90/10)	0.6ml (10% PEG, 8,000)	160 mg bupivacaine pamoate*
R.	1g (95/5)		160 mg amikacin sulfate
S.	1g (95/5)	0.6 ml 10% PS80	240 mg amikacin pamoate*
T.	1g (95/5)	0.6 ml 10% PEG, 800	doxycycline HCl
U.	1g (95/5)	0.6 ml 10% PS80	doxycycline pamoate*
V.	1g (95/5)	0.6 ml 10% PS80	clindamycin pamoate*

* includes complexing agent

Production

The production of the delivery system can be illustrated as follows:

$CaSO_4$-1/2 H_2O + matrix polymer solution + bioactive agent

⇓

Slurry

⇓

Solid

When contacted with water calcium sulfate hemihydrate is converted to the dihydrate, $CaSO_4$- 2 H_2O, which crystallizes. The mass of needle-like crystals produces a porous matrix with high compressive strength, as much as 1200 psi or more. A conditioning agent such as calcium stearate can be pre-mixed with the calcium sulfate hemihydrate.

The slurry can be injected into the desired location with solidification *in situ.* This composition is ideal for dental and orthopedic applications. The fact that the slurry can set-up in the presence of moisture is very advantageous.

A delivery system can be produced by:

blending of an inorganic substance such as calcium sulfate hemihydrate and optionally a conditioning agent such as calcium stearate, both in powder form,
mixing with matrix polymer solution (the active agent can be dissolved or suspended in the polymer solution or the solid drug can be finely ground in the presence of the calcium sulfate hemihydrate),

solidification in a mold or in bulk, and
preparing of microbeads by milling and sizing.

Molds made of stainless steel or teflon can be used to prepare beads, cylinders, spheres (e.g., 3mm in diameter), wafers etc. Microbeads can in turn be compressed into tablets with various binding agents to yield another dosage form.

The composition is used in the manufacture of top dressing, a feed pellet, etc.

* * *

Administration

Administration of the solid matrix can be by surgical implant, oral, i.p., i.a. or p.a. The liquid injection can be s.c., i.m, or i.p. Advantageously, the administration is done by parenteral injection.

a. Cement
1g of calcium sulfate/calcium stearate (1-25% w/w) plus amikacin pamoate (100-320mg) are thoroughly mixed and contacted with 0.6 ml of aqueous dextran sulfate (10% w/v). After blending to a smooth slurry (30s), the material is transferred to a 5ml syringe and installed *in vivo* where it solidifies. Amikacin sulfate can be blended with amikacin pamoate to adjust the release profile. Presence of the calcium stearate allows for the solidification in the presence of moisture.

b. Beads/Cylinders
Sterile 3mm beads can be installed individually with mosquito forceps or in groups using a cannula. A teat cannula is a safe tool for installation of beads and cylinders. This approach has been successfully used in the treatment of squamous cell carcinoma via intralesional chemotherapy with 3mm beads of the invention containing *cis*-Pt (7%).

c. Microbeads

Injection
Sterile microbeads (45-150microns) (dry) are suspended in a suitable liquid for injection just prior to use. When antibiotics are involved, a solution of the antibiotic of choice may be used as the suspending liquid. For example, in treating a septic joint, amikacin solution (3ml/25%) is used to suspend microbeads (300mg) containing amikacin pamoate prepared as described in Example 4. An "initial burst" provided by the soluble amikacin sulfate is followed by the amikacin that elutes from the microbeads. A similar approach is appropriate for creating a subcutaneous depot of antibiotics and other active ingredients.

Oral

Microbeads are mixed with food or feed. The composition of the invention is tasteless and in some cases will mask the taste of a bioactive compound. In addition, the microbeads of the invention can be included in a capsule for oral delivery.

* * *

Top Dressing

In one embodiment of the invention, the delivery system in the form of microgranules or other shapes is added to or mixed with food or feed (as used herein the term "feed" includes food). The delivery system is tasteless and odorless and in some cases will mask the taste of a bioactive compound. The delivery system can be added to or mixed with pet food, human food (treat for a companion animal), sweet feed, (a mixture of molasses, cracked corn, oats, etc), fish food, and poultry feed mixes. The delivery system is added or sprinkled on top as a top-dressing and advantageously, the delivery system is added to moist feed or food so that it does not settle to the bottom of the food or feed container. Alternatively, the delivery system is added to the dry food or feed in a form that will adhere to the food or feed. Dosing is typically 100-300 microgram/kg for ivermectin. The powdered formulation dosed at the same interval and amount accepted in the field, is mixed with the food for a given animal.

Feed Pellets

The delivery system can also be incorporated in a feed pellet, as in the case for livestock, horses, fish, etc. The feed pellet typically includes one or more of ground alfalfa, corn, or other grain. The ingredients are mixed with water and then extruded into a dry pellet, tablet (optionally chewable, or biscuit. Common rabbit feed is an example of a feed pellet form. The feed pellet can also include meat by-products. The ingredients are mixed in a slurry, and pressed into a pellet or tablet for administration.

Salt or Mineral Blocks

The delivery system can also be incorporated in a salt or mineral block, as in the case for livestock, deer, elk etc. The block typically includes sodium chloride, minerals and the delivery system.

* * *

Horses

In the case of horses, feeding is advantageously achieved by mixing the active agent composition (such as ivermectin) with sweet feed. Usually a one pound can of molasses-containing grain mix is adequate. Fasting overnight prior to morning feeding can be beneficial. Care should be taken to assure that the horse gets the medicated feed. Usually

this is achieved by isolating dominant horses or horses that eat very fast and then bother other horses. Feeding horses in individual box stalls (enclosures) eliminates the concern for one horse getting too much or too little. Nose bags can also be employed.

One embodiment of the invention is a dry, micro-granular formulation of ivermectin that is administered by mixing with the horse's grain ration, preferably in sweet feed although other moist formulations will work as well.

The advantages of the dry formulation over the paste and liquid include:

-No head restraint of the horse is required
-More reliable dosing—the treated feed has been readily accepted in all cases studied
-Safer for veterinarian, horse owner, or stable worker
-Safer for the horse—no risk of injury due to resisting the paste or liquid syringe
-More convenient, faster administration.

Livestock

Feeding of livestock is accomplished by mixing the delivery system with feed as a top dressing or as a pre-mix, or incorporating the delivery system in a feed pellet for dosing. This mixture of the delivery system in large quantities of feed is then fed to cattle or other ruminants on an individual basis. This method improves palatability and is an alterative to injectable parasiticide formulations or oral "gun" dosing of a liquid. The method can be used with cattle, sheep and goats.

Wildlife

Feeding of wildlife such as deer or elk can be achieved in the same manner as for livestock or by using a salt or mineral block.

Poultry

For poultry such as chicken or turkey, the delivery system including the active ingredient such as ivermectin, is administered by spreading it on the housing floor as grit. In one embodiment, 3mm beads are colorized (eg red) to increase demand by the birds. In another embodiment, the delivery system is included in the pelletized feed.

Pets

For domestic animals (egs dogs, cats) the delivery system (including eg ivermectin) is applied, for example, in a microgranular form at the recommended dosage, as a top dressing, or mixed with the animals' food, or added to a human food product and given to the pet as a treat. The invention presents an advantage to the pet owner in ease of administration and

acceptance of the treatment such as monthly heartworm treatment (ivermectin/pyrantel)(all year round).

The pet can receive the delivery system, which includes the active ingredient in a number of ways:

- Sprinkled on top of the pet food
- Mixed in with the pet food
- Mixed in an amount of human food and given as a treat
- Incorporated by the manufacturer in the feed (feed pellet, chewable tablet, biscuit).

Fish

For fish (eg. salmon), the delivery system is incorporated in a feed pellet for administration.

* * *

The following Examples are illustrative, but not limiting of the compositions and methods of the present invention. Other suitable modifications and adaptations of a variety of conditions and parameters normally encountered which are obvious to those skilled in the art are within the spirit and scope of this invention.

Examples

Example 1

Synthesis of amikacin pamoate

Disodium pamoate (865mg) was dissolved in a minimum amount of water. Amikacin sulfate (782 mg), dissolved in a minimum amount of water, was added to the sodium pamoate solution and mixed thoroughly at room temperature. The precipitate was collected by filtration and washed with two portions (5ml) of cold water. The material was dried in a vacuum dessicator for 48 hrs.
Yield: 70 %. MP: 235-244 degrees C with decomposition.

Example 2

Synthesis of clindamycin pamoate

Disodium Pamoate (216mg) was dissolved in a minimum amount of water. Clindamycin-HCl (461 mg), dissolved in a minimum amount of water, was added to the sodium pamoate solution and mixed thoroughly at room temperature. The precipitate was collected by filtration and washed with two portions (5ml) of cold water. The material was dried in a vacuum dessicator for 48 hrs.
Yield: 78 %. MP: 189-194 degrees C.

Example 3

Preparation of calcium sulfate/calcium stearate formulation containing enrofloxacin

Calcium sulfate and calcium stearate powders were thoroughly mixed in a weight ratio of 19/1. This mixture (1g) was then blended with finely ground enrofloxacin (160mg). To this solid mixture was added 0.6ml of polyethyleneglycol solution (PEG-MW 8,000, 10%w/v). The slurry was mixed for one minute and then allowed to solidify in bulk or was injected into a teflon mold for the production of 3mm beads.

Example 4

Formulation containing amikacin pamoate

To calcium sulfate (1g) was added 0.16g of amikacin pamoate which had been finely ground. The powders were thoroughly mixed and contacted with 0.6 ml of PEG-8000 (10% w/v). After mixing for about 1 min, the slurry was injected into a mold or allowed to solidify in bulk. An identical procedure is used with calcium sulfate hemihydrate containing 5% calcium stearate. Another variation which produces a convenient preparation is to add 10% (w/v) of polysorb 80 to the 10% PEG-8000.

Example 5

Formulation of clindamycin pamoate

This procedure was identical to Example 3 except that clindamycin pamoate (160mg) was substituted for enrofloxacin.

Example 6

Formulation of cefoperazone

Calcium sulfate and calcium stearate powders were thoroughly mixed in a weight ratio of 19/1. This mixture (0.8g) was then blended with finely ground cefoperazone (200mg). To this solid mixture was added 0.6ml of polyethyleneglycol solution (PEG-MW 8,000, 10%w/v). The slurry was mixed for one minute and then allowed to solidify in bulk or was injected into a teflon mold for the production of 3mm beads.

Example 7

In vitro release profiles (3mm beads)

Four 3mm beads were incubated in 0.4 ml of PBS, pH 7.4 at 37C. The PBS buffer was changed at 24-hour intervals over a 4-day period and the samples were analyzed for eluted drug either spectrophotometrically or by microbiological assay. Representative results are shown below.

A. Amikacin pamoate

Day	%Released
1	33
2	14
3	3.3
4	2.9

B. Clindamycin pamoate

Day	%Released
1	5.7
2	5.7
3	5.7
4	5.7

Enrofloxacin

Day	%Released
1	2.4
2	2.4
3	2.4
4	1.9

Cefoperazone

Day	%Released
1	11
2	10
3	6
4	6

Example 8

In vitro release profile with microbeads (45-150 microns)

Cefoperazone microbeads were prepared as described in Example 6 (solidification in bulk). Milling and sieving the solid matrix produced the microbeads. Microbeads (100mg) were incubated in 0.4 ml of PBS, pH 7.4 at 37C. The PBS buffer was changed at 24-hour intervals over a 4-day period and the samples were analyzed for eluted drug either spectrophotometrically or by microbiological assay. Results are shown below.

A. Release of antibiotic from Cefoperazone microbeads.

Day	%Released
1	15
2	11
3	11
4	16

B. Release of antibiotic Enrofloxacin microbeads (10% enrofloxacin, 5% calcium stearate, 10% PEG).

Day	%Released
1	9.8
2	6.6
3	10.2
4	10.2

Example 9

Use of Formulation of amikacin pamoate microbeads to treat an equine joint infection

Five-year-old, TB gelding presented with a septic left rear hock joint, which resulted from a puncture wound. Lameness was grade 5—non-weight-bearing. Prior therapy included systemic treatment with penicillin and gentamicin without effect. The joint fluid showed elevated protein and WBC. Culture revealed *S. Aureus*. Following joint lavage, a suspension containing 300 mg of amikacin pamoate microbeads was injected through an 18-gauge needle. The horse showed rapid improvement and the joint fluid was found to be sterile at day three. At five days post treatment, the horse was sound.

Example 10

Treatment of osteomyelitis using formulation of amikacin pamoate

A one-year old Connemara filly presented with osteomyelitis/joint sepsis in the right hind coffin joint. Three days of systemic treatment with ampicillin plus gentamycin produced no improvement. Following debridement, 1g of formulation (5% calcium stearate, described in Example 4) was injected in the lesion following lavage with lactated Ringer's solution. For injection the cement was loaded into a five-ml syringe after 30s of mixing time.

Heat and swelling receded after two days. The horse was sound ten days post-treatment. Three months post-treatment, owners said the horse was 100% sound.

Example 11

Treatment of osteomyelitis and septic tendon sheath

A three-year-old Arab filly presented with osteomyelitis of the talus with an accompanying septic tendon sheath. Prior treatment consisted of i.m. injections of penicillin for 5 days with no result. The osteomyelitic lesion was curetted; the tendon sheath was debrided and flushed.

Five holes (3.2mm x 4mm deep) were drilled in the talus. The holes were filled with the formulation of amikacin pamoate as described in Example 10. Effusion diminished and the horse became completely sound. Follow-up at 3 months and 11 months revealed that the horse successfully returned to intended use.

Example 12

Antibiotic Depot/formulation of clindamycin pamoate plus unformulated clindamycin pamoate. Treatment of an upper respiratory infection

A mixed-breed dog (20 lb, age 5) was treated for a chronic respiratory infection with clindamycin pamoate. The formulation of clindamycin-pamoate was co-administered with unformulated clindamycin pamoate to provide a long-lasting depot. Finely ground clindamycin pamoate (100mg) was mixed with the formulation of clindamycin pamoate (1.7g, Example 5). The mixture was suspended in sterile water and injected, s.c., in two portions on either side of the neck. The animal was asymptotic after four days.

Example 13

Treatment of an infected bite with clindamycin pamoate

An English foxhound pup (10lb) suffered from an infected bite on the right forelimb. Culture revealed a mixed infection with anaerobes. Unformulated clindamycin pamoate (150mg) was suspended in sterile water and injected, s.c., in the scruff of the neck. The hound's temperature returned to normal on the third day post treatment. After 6 days without further treatment the hound's leg showed very little swelling and the lameness disappeared.

Example 14

Synthesis of doxycycline pamoate

Disodium Pamoate (54 mg) was dissolved in a minimum amount of water. Doxycycline-HCl (120 mg), dissolved in minimum amount of water, was added to the sodium pamoate solution and mixed thoroughly at room temperature. The precipitate was collected by filtration and washed with two portions (5 ml) of cold water. The material was dried in a vacuum dessicator for 48 hors.
Yield: 85%. MP: 190-196°.

Example 15

Formulation containing doxycycline pamoate

To calcium sulfate (1g) was added 0.16g of doxycycline pamoate which had been finely ground. The powders were thoroughly mixed and contacted with 0.6 ml of PEG-8000 (10% w/v). After mixing for about 1 min, the slurry was injected into a mold or allowed to solidify in bulk. An identical procedure is used with calcium sulfate hemihydrate containing 5% calcium stearate. Another variation which produces a convenient preparation is to add 10% (w/v) of Polysorb 80 to the 10% PEG-8000. As a cement, this formulation is useful in treating periodontal defects. In this case, the slurry is transferred to the barrel of a 5 ml syringe and installed through a 14 gauge needle with a blunt end.

Example 16

Formulation with thrombin/fibrinogen

Fibrinogen can be used as the matrix polymer when thrombin is included in the formulation—thrombin converts fibrinogen to fibrin which polymerizes. The amount of thrombin and fibrinogen can be adjusted to provide a gelation time that is longer than the setting time of the inorganic matrix. This sequence results in a matrix within a matrix. Thrombin (1mg) is mixed with 4.7 g of calcium sulfate/calcium stearate (19/1) to yield a stock (solid) solution. This solid is then diluted, as appropriate, to give 0.1 units of thrombin/gram of calcium sulfate/calcium stearate.

Erythropoietin (4.5mg) is mixed with 1g of calcium sulfate/calcium stearate/thrombin (0.1 units). To this solid is added 300ul of a solution containing fibrinogen (6%) and serum albumin (5%). The fibrinogen/serum albumin solution is made with Hepes buffer (0.03M, pH 7.2). After 48 hrs the hard solid is milled and sized to 45-150 microns.

Similar preparations can be made with other bioactive polypeptide hormones, antigens, antibiotics, and other bioactive compounds.

Example 17

Formulations with cross-linked albumin (gelatin)

One g of calcium sulfate/calcium stearate (19/1) is mixed with 160 mg of finely ground enrofloxacin. To this solid is added 300ul of 3% serum albumin and 300ul of glutaraldehyde solution (0.25%). Mixing for 30s yields a smooth slurry which is poured into a tray; the material is allowed to dry for 48 hrs at room temperature. The hard solid is milled and sized to the range of 45-150 microns. A 3% solution of gelatin can be substituted for the serum albumin solution. Other useful matrix polymers include chitosan, *bis*-amino-PEG, polypeptides containing lysine, and other biocompatible polymers which contain electrophilic functional groups. Use of cross-linked matrix polymer is especially appropriate for preparing formulations for the long-term, continuous delivery of antigens.

Example 18

Formulation and Use of Ivermectin

Ivermectin (110mg) was finely ground and combined with calcium sulfate hemihydrate (890mg) that contained 5% calcium stearate w/w. After thorough mixing, 0.6ml of polyethyleneglycol solution (PEG-MW 8,000, 10%w/v) was added. After solidification, the product was allowed to stand for 24 hr, milled and sized (45-150 microns). The material ("Ivermectin System") was used to successfully deworm horses at a dosage of ivermectin of 200 mcg/kg.

Table 2. Treatment of parasites in naturally infected horses—eggs per gram of feces as a function of time. EPG was determined at Day-5, day 7, and day 14. Five animals were included in each group.

	Mean EPG			
Subject Group (5 animals)	day-5	day 7	day 14	day 28
Untreated Controls	230	334	246	391
Positive Controls-Eqvalan (Merial)	320	<1	<1	11
Ivermectin System	262	<1	<1	1

Example 19

Two groups of horses (mixed breed, ages 5-15, weights 800-1300lb) were treated with ivermectin preparations to demonstrate the relative efficacy of the preparation. Five days before administration fecal samples were taken for determination of Strongyl eggs per gram (EPG). At day 0 ivermectin was administered at a dosage of 200ug/kg. Eqvalan (Merial) paste was administered as directed. Ivermectin System was sprinkled of sweet feed and mixed prior to feeding. The top-dressed feed was well accepted by the horses and was completely consumed. Sweet feed is a commercial product of mixed grains and nutrients which is impregnated with molasses. The Ivermectin System powder sticks to molasses and is incorporated into the mix. For a 1250lb horse 1.68g of powder are used with 1lb of sweet feed. Results are shown in below.

Treatment of parasites in naturally infected horses—eggs per gram (EPG) of feces as a function of time. EPG was determined at day -5, day +7, and day +14. Five animals were included in each group. Treatment was at day 0.

	Mean EPG		
Subject Group (5 animals each)	day -5	day +7	day +14
Untreated Controls	230	334	246
Positive Control-Eqvalan (Merial)	320	<1	<1
Ivermectin System	262	<1	<1

Plasma concentrations were determined using HPLC following administration of Eqvalan paste and two versions of Ivermectin System. Blood samples (6) were drawn at timed

intervals and analyzed for ivermectin. Ivermectin System 1 compared favorably with Eqvalan. This preparation contained PEG-8000 as the matrix polymer. Ivermectin System 2 contained PS80 as the matrix polymer. These results demonstrate the ability to control the distribution of active ingredient. More ivermectin is relation in the digestive tract with PS80 as the matrix polymer as compared to the formulation containing the PEG-8000.

* * * *

It will be readily apparent to those skilled in the art that numerous modifications and additions may be made to both the present invention, the disclosed device, and the related system without departing from the invention disclosed.

What is claimed is:

1. A matrix delivery system comprising:
a) calcium sulfate, and
b) a conditioning agent,
wherein said calcium sulfate of said matrix delivery system becomes a solid by hydration, and wherein said conditioning agent is present in the range of 5-30% (w/w) based on calcium sulfate.
2. A system as in claim 1, further comprising an antiparasitic.
3. A system as in claim 1, further comprising a matrix polymer.
4. A system as in claim 3, wherein the matrix polymer is a biopolymer selected from the group consisting of hyaluronic acid, chondroitin sulfate, dextran, dextran sulfate, polyethylene glycol and protein.
5. A system as in claim 1, wherein said conditioning agent is selected from the group consisting of calcium stearate, zinc undecylenate, magnesium palmitate, sodium laurate, calcium napthenate, calcium oleate, lauryl ammonium sulfate.
6. A system as in claim 1, wherein said conditioning agent is calcium stearate.
7. A system as in claim 1, further comprising a complexing agent selected from the group consisting of chondroitin sulfate, polyglutamic acid, polyaspartic acid, pamoic acid, polynucleotides, a cationic polypeptide, cyclodextrin, polyoxyethylene alcohol, ester or ether, and defatted albumin.
8. A system as in claim 7, wherein said polyoxyethylene alcohol, ester or ether is a surfactant.
9. A system as in claim 7, wherein said cyclodextrin is hydroxypropyl beta cyclodextrin.
10. A system as in claim 7, wherein said complexing agent is a lipid or a liposome.
11. A system as in claim 10, wherein said lipid is a lipid of biological origin selected from the group consisting of cholesterol and lecithin.
12. A system as in claim 2, comprising calcium sulfate, calcium stearate, and a glycosaminoglycan.
13. A system as in claim 12, wherein said glycosaminoglycan is hyaluronic acid or chondroitin sulfate.
14. A system as in claim 1, wherein said system is in the form of a bead, a wafer, a tablet, a sphere, a granule or a cylinder.
15. A system as in claim 1, wherein said conditioning agent contains a hydrophobic moiety.
16. A system as in claim 1, comprising calcium sulfate, calcium stearate and hyaluronic acid.
17. A system as in claim 1, further comprising a medicinal.
18. A system as in claim 17, wherein said medicinal is a salt.
19. A composition comprising a system as in claim 17, and a soluble medicinal.
20. A composition comprising a system as in claim 17, and a medicinal and a complexing agent.
21. A composition as in claim 19, comprising
a) a matrix containing calcium sulfate, calcium stearate, amikacin, and
b) amikacin sulfate.
22. A composition as in claim 20 comprising
a) a matrix containing calcium sulfate, calcium stearate, amikacin, and
b) amakacin pamoate.
23. A composition as in claim 21, further comprising amikacin sulfate.

24. A system as in claim 17, wherein said medicinal is a drug precursor.
25. A system as in claim 17, wherein said medicinal is a protein medicinal.
26. A system as in claim 17, wherein said medicinal is an anti-infective selected from the group consisting of gentamicin, clarithromycin, doxycycline, minocycline and lincomycin, amikacin, penicillin, cefazolin, ciprofloxacin, enrofloxacin, norfloxacin, silver sulfadiazine, imipenem, piperacillin, nafcillin, cephalexin, cefoperazone, vancomycin, tobramycin, nystatin, silver sulfadiazine, imipenem, and amphotericin B or salts thereof.
27. A system as in claim 17, wherein said medicinal is an antibiotic.
28. A system as in claim 17, wherein said medicinal is an antineoplastic agent.
29. A system as in claim 17, wherein said medicinal is an anesthetic.
30. A system as in claim 29, wherein said anesthetic is lidocaine.
31. A system as in claim 30, wherein the lidocaine is selected from the group consisting of lidocaine hydrochloride and lidocaine pamoate.
32. A system as in claim 1, further comprising a non-medicinal compound.
33. A system as in claim 32, wherein said non-medicinal compound is selected from the group consisting of a sterilant, a pheromone, a herbicide, a pesticide, an insecticide, a fungicide, an algicide, a growth regulator, a nematicide, a repellent, and a nutrient.
34. A system as in claim 33, further comprising a herbicide.
35. A system as in claim 32, wherein said matrix polymer is selected from the group consisting of polyethyleneglycol, polyvinylpyrrolidone, polyvinylalcohol, starch, xanthan, cellulose and a cellulose derivative.
36. A system as in claim 32, wherein said complexing agent is a complexing agent selected from the group consisting of a polyoxyethylene ester or ether, and a surfactant of either biological or non-biological origin.
37. A system as in claim 32, wherein said complexing agent is selected from the group consisting of polyacrylic acid, alginic acid, dextran sulfate, polyvinylpyridine, chitosan, polyvinylamine, polyethyleneimine and a lipid.
38. A system as in claim 1, wherein said system is porous.
39. A system as in claim 3, wherein said matrix polymer is dextran sulfate.
40. A system as in claim 3, wherein said matrix polymer is polyethyleneglycol.
41. A system as in claim 39, further comprising amikacin.
42. A system as in claim 39, further comprising silver sulfadiazine.
43. A composition comprising amikacin sulfate and amikacin pamoate.
44. A method of producing sustained release of a medicinal in a mammal comprising administering the system of claim 1 and a medicinal to said mammal.
45. A method as in claim 44, wherein said administration is by subcutaneous injection.
46. A method of treating infection in a mammal comprising administering a composition comprising the system of claim 1 and an anti-infective to said mammal.
47. A method as in claim 46, wherein said anti-infective is selected from the group consisting of gentamicin, clarithromycin, doxycycline minocycline and lincomycin, amikacin, penicillin, cefazolin, ciprofloxacin, enrofloxacin, tobramycin, norfloxacin, silver sulfadiazine, imipenem, piperacillin, nafcillin, cephalexin, vancomycin, nystatin, and amphotericin B or salts thereof.
48. A method of producing a delivery system comprising mixing
(a) calcium sulfate, (b) a matrix biopolymer, and (c) a conditioning agent, wherein said conditioning agent is present in the range of 5-30% (w/w) based on calcium sulfate.

49. A method as in claim 48, wherein said inorganic compound, and conditioning agent are premixed and then added to said matrix biopolymer.
50. A method of scaffolding bone or filling a defect in bone comprising administering to said bone the delivery system of claim 1.
51. A method as in claim 50, wherein said delivery system further comprises freeze-dried bone.
52. A method of administering a delivery system comprising:
a) mixing calcium sulfate, a conditioning agent in the range of 5-30% (w/w) based on calcium sulfate, and a medicinal to form a slurry;
b) administering said slurry to said mammal,
wherein said slurry solidifies after administration.
53. An antibiotic selected from the group consisting of amikacin pamoate, clindamycin pamoate and gentamicin pamoate.
54. A method of producing a delivery system comprising mixing:
a) an inorganic compound capable of undergoing hydration and/or crystallization, a conditioning agent and thrombin,
b) fibrinogen,
wherein mixing (a) and (b) converts fibrinogen to fibrin.
55. A feed composition comprising:
a) feed,
b) a solid composition comprising an active agent dispersed throughout a solid matrix hydration reaction product of an aqueous mixture comprising said active agent, an inorganic compound capable of undergoing hydration, a conditioning agent, and/or a matrix polymer, and/or a complexing agent.
56. A composition as in claim 55 including a matrix polymer, wherein said matrix polymer is a biopolymer selected from the group consisting of hyaluronic acid, chondroitin sulfate, dextran, dextran sulfate, polyethylene glycol and protein.
57. A composition as in claim 55, including a conditioning agent, wherein said conditioning agent is selected from the group consisting of calcium stearate, zinc undecylenate, magnesium palmitate, sodium laurate, calcium napthenate, calcium oleate, lauryl ammonium sulfate.
58. A composition as in claim 57, wherein said conditioning agent is calcium stearate.
59. A composition as in claim 55, including a complexing agent wherein said complexing agent is selected from the group consisting of chondroitin sulfate, polyglutamic acid, polyaspartic acid, pamoic acid, polynucleotides, a cationic polypeptide, cyclodextrin, polyoxyethylene alcohol, ester or ether, and defatted albumin.
60. A composition as in claim 56, wherein said solid composition comprises calcium sulfate, calcium stearate, and a glycosaminoglycan.
61. A composition as in claim 60, wherein said glycosaminoglycan is hyaluronic acid or chondroitin sulfate.
62. A composition as in claim 55, wherein said solid composition is in the form of a bead, a wafer, a tablet, a sphere, a granule or a cylinder.
63. A composition as in claim 61, wherein said solid composition comprises calcium sulfate, calcium stearate and hyaluronic acid.
64. A composition as in claim 55, wherein said active agent is a medicinal.
65. A composition as in claim 64, wherein said medicinal is an anti-infective selected from the group consisting of lincomycin, penicillin, ciprofloxacin, enrofloxacin, norfloxacin, nafcillin, cephalexin, and orally active cephalosporin.
66. A composition as in claim 64, wherein said medicinal is an antibiotic.

67. A composition as in claim 64, wherein said medicinal is an antiparasitic.
68. A composition as in claim 67, wherein said antiparasitic is ivermectin.
69. A composition as in claim 55, wherein said active agent is selected from the group consisting of a sterilant, a pheromone, a growth regulator, a nematicide, a nutriceutical, a repellent, a vitamin, and a nutrient.
70. A composition as in claim 55, including a matrix polymer wherein said matrix polymer is selected from the group consisting of polyethyleneglycol, polyvinylpyrrolidone, polyvinylalcohol, starch, xanthan, cellulose and a cellulose derivative.
71. A composition as in claim 70, wherein said matrix polymer is polyethyleneglycol.
72. A composition as in claim 55 in the form of a feed pellet.
73. A composition as in claim 55 in the form of a salt or mineral block.
74. A composition as in claim 55 in the form of a dog biscuit.
75. A composition as in claim 55 in the form of a chewable tablet.
76. A method of delivering an active agent to a mammal comprising administering the feed composition of claim 55 to said mammal.
77. A method of treating or preventing an infection in a mammal comprising administering a composition comprising the system of claim 55 to said mammal wherein said active agent is an antiinfective.
78. A method as in claim 77, wherein said anti-infective is selected from the group consisting of lincomycin, penicillin, ciprofloxacin, enrofloxacin, norfloxacin, nafcillin, cephalexin, orally active cephalosporin.
79. A method of treating or preventing a parasitic infection in a mammal comprising administering a composition comprising the feed composition of claim 55 wherein said active agent is an antiparasitic to said mammal.
80. A method as in claim 79, wherein said anti-parasitic is selected from the group consisting of ivermectin or moxidectin.
81. A method as in claim 80 wherein said mammal is a horse.
82. A method as in claim 80 wherein said mammal is a cow.
83. A method as in claim 80 wherein said mammal is a chicken.
84. A method of producing a feed composition comprising mixing
a) feed, and
b) a solid composition comprising an active agent dispersed throughout a solid matrix hydration reaction product of an aqueous mixture comprising said active agent, an inorganic compound capable of undergoing hydration, a conditioning agent, and/or a matrix polymer, and/or a complexing agent.
85. A method of deworming a horse comprising:
mixing sweet feed and a solid composition comprising ivermectin dispersed throughout a solid matrix hydration reaction product of an aqueous mixture comprising ivermectin, calcium sulfate hemihydrate, and polyethylene glycol, administering said mixture to said horse.
86. A method of deworming a dog comprising:
mixing dog food and a solid composition comprising ivermectin dispersed throughout a solid matrix hydration reaction product of an aqueous mixture comprising ivermectin, calcium sulfate hemihydrate, and polyethylene glycol, administering said mixture to said dog.

87. A method of deworming a cat comprising:
mixing cat food and a solid composition comprising ivermectin dispersed throughout a solid matrix hydration reaction product of an aqueous mixture comprising ivermectin, calcium sulfate hemihydrate, and polyethylene glycol,
administering said mixture to said cat.